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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER

ART UNIT	PAPER NUMBER
	14

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/589,483	Applicant(s) SUKHATME, VIKAS P.	
	Examiner Konstantina Katcheves	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6,8,9,14-17,22,23,25 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *9*.
4)☐ Interview Summary (PTO-413) Paper No(s). _____.
5)☐ Notice of Informal Patent Application (PTO-152)
6)☒ Other: *detailed action*.

DETAILED ACTION

Claims 1-39 are pending in the instant application.

Election/Restrictions

Applicant's election without traverse of group V in Paper No. 7 is acknowledged. Claims 5, 7, 10-13, 18-21, 24, 27-35, 37 and 39 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 7. Accordingly, claims 1-4, 6, 8, 9, 14-17, 22, 23, 25, 26, 36 and 38 have been examined.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Page 18 of the specification contains embedded hyperlinks. Applicant is required to delete any embedded hyperlinks and/or other forms of browser-executable code. The attempt to incorporate subject matter into the patent application by reference in this manner is considered to be an improper incorporation by reference. See MPEP § 608.01

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who

has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1-4, 8, 9, 14-16, 22 and 25 are rejected under 35 U.S.C. 102(e) as being anticipated by Davidson (US Patent No. 6,057,122).

The invention of the instant claims is drawn to a method of making anti-angiogenic proteins, mutants, fragment, derivatives and fusion proteins thereof comprising transforming *Pichia pastoris* with an expression vector. The expression vector contains a multiple cloning site, and His.Tag motif wherein the protein produced also comprises a histidine tag motif.

Davidson discloses a method of producing a protein for the purposes of treating anti-angiogenesis, kringle which is capable of inhibiting angiogenesis related disease. Kringle, disclosed by Davidson, comprises amino acid sequences having substantial seuqence homology with human plasminogen and exhibits anti-angiogenic activity. See column 5. The method disclosed in Davidson comprises transforming a *P. pastoris* host with an expression vector that contains the DNA encoding the protein of interest, a multiple cloning site and a His.Tag motif. See Figure 5, column 1, and Example 19.

The expression vectors disclosed by Davidson share similar properties with the expression vectors recited in the instant application. The vector disclose by Davidson comprises, for example, a nucleic acid sequence encoding the anti-angiogenic protein of interest, cloning sites including EcoRI and XhoI, histidine tag motif, colE1, AOX1 and ampicillin resistance, among other regions. The essential elements of the plasmid disclosed by Applicant also comprise an anti-angiogenic protein of interest, cloning sites including EcoRI and XhoI, a histidine tag motif, colE1, AOX1 and antibiotic, zeocin, resistance. Therefore, sufficient evidence of similarity is present to shift the burden to Applicant to provide evidence that the

claimed products are unobviously different than the method and expression vectors disclosed in the reference described above. *In re Best*, 195 USPQ 430 (CCPA 1977).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 6 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davidson.

The instant invention is relied upon as described above and further comprising a fusion protein at a concentration of 10-20 milligrams or more per liter of culture fluid.

Davidson is relied upon as described above. However, Davidson fails to quatify his yields and show a protein concentration of at least 10-20 milligrams.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the method disclosed by Davidson to produce the product protein at a concentration of at least 10-20 milligrams. Davidson teaches that *P. pastoris* transformed by the plasmid described above were grown in 5 ml of BMGY medium with ampicillin at 29 degrees overnight. Applicant's method discloses that their *P. pastoris* cells transformed with pPICZαA were grown in 25 ml of BMGY with zeomycin for 16-24 hours at 30 degrees. However, Applicant further grows the cells in 500 ml of medium in a two liter flask for 2-3 days. The ordinary skilled artisan would reasonably expect to get comparable yields to those disclosed by

Applicant for several reasons. First, the plasmids disclosed by Davidson and Applicants plasmid are substantially similar. Second both Davidson and applicant transform the same cells, *P. pastoris*, with their respective plasmids. Third, the culture conditions disclosed by Davidson are almost identical to those used by Applicant. It is well within the purview of the ordinary skilled artisan to further culture the cells Davidson on a larger scale and expect comparable yields. Therefore, absent evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Claims 23, 26, 36 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over either O'Reilly et al. (WO 97/15666) (O'Reilly) or Hägg et al. (Genomics Vol.45 1997) (hereinafter "Hägg") in view of Davidson.

The invention of the instant claims is drawn to a method of making the anti-angiogenic protein, restin and mutant, derivative, fragment or fusion protein thereof comprising transforming *Pichia pastoris* with an expression vector. The expression vector contains a multiple cloning site, and His.Tag motif wherein the protein produced also comprises a histidine tag motif.

O'Reilly teaches an inhibitor of cell proliferation capable of inhibiting angiogenesis that is approximately 20 kDa and corresponds to the C-terminal fragment of collagen type XVIII and a method of making said inhibitor.

Hägg teaches collagen type XV and discloses that the C-terminal regions of collagen type XVIII and XV are highly homologous and similar in their overall domain structure and a mthod

of making collagen type XV. Both Hägg and O'Reilly fail to teach methods of producing the proteins disclosed using *P. pastoris* and the plasmid described in the specification.

Davidson is relied upon as described above. However, Davidson fails to teach a method of making an anti-angiogenic protein wherein the protein is restin, or a mutant, derivative, fragment or fusion protein thereof.

It would have been obvious to one of ordinary skill in the art to make restin by tranforming *P. pastoris* cells with a plasmid encoding the anti-angiogenic protein because either the C-terminal fragment of collagen type XVIII, disclosed in O'Reilly, or collagen type XV, disclosed by Hägg, is encompassed by Applicant's claims. Applicant claims restin and any mutant, derivative, fragment or fusion protein thereof. Applicant's disclosure defines restin as the C-terminal region of collagen type XV approximately 20 kDa. Because the C-terminal region of collagen type XVIII is highly homologous to that of collagen type XV, the protein disclosed in O'Reilly is a mutant or derivative of the protein recited in Applicant's claims. Moreover, absent evidence to the contrary, Hägg discloses collagen type XV, which comprises the C-terminal sequence of restin described by Applicant.

The ordinary skilled artisan would have been motivated to use the method disclosed in Davidson to make the proteins disclosed in either O'Reilly or Hägg for the purposes of sequence and genetic analysis or for the purposes of treating angiogenesis. O'Reilly even suggests making the protein recombinantly using a microorganism. See O'Reilly page 20. The ordinary skilled artisan would reasonably expect a *P. pastoris* host cell to express the proteins disclosed in O'Reilly and Hägg because of the versatility of yeast as expression systems. Furthermore, as disclosed in Davidson yeast provide the ordinary skilled artisan with a superior host cell for

expression because of advantageous protein processing, protein folding and post-translational modification inclusive of glycosylation. Therefore, absent evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Claim Rejections - 35 USC § 112

First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 6, 8, 9, 14-17, 22, 23, 25, 26, 36 and 38 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims recite sequences of anti-angiogenic proteins with undefined modifications, which have certain activities or functions. These are genus claims that encompass a wide array of molecules. The specification does not disclose any of the variants or modifications, nor does it provide any teachings as to how the structures of these sequences relate to their function. Thus, the specification does not describe the complete structure of a representative number of species. Neither does the specification describe a representative number of species in terms of partial structure and relevant identifying characteristics. Absent of

such teachings and guidance as to the structure-function relationship of these molecules, the specification does not describe the claimed recombinant DNA molecules in such full, clear, concise and exact terms so as to indicate that Applicant had possession of these molecules at the time of filing of the present application. Thus, the written description requirement has not been satisfied.

The claims are broadly drawn to a method for providing producing a biologically active anti-angiogenic protein or any mutant, fragment, fusion protein or variant thereof.

The specification is not enabled for any mutant, fragment, fusion protein or variant of an anti-angiogenic protein and specifically restin. A multitude of mutants and variants may be generated that may or may not have the desired activity. The specification does not provide any guidance on which fragments may retain the anti-angiogenic activity or what motifs are required for said activity. Applicant, thereby, fails to show that he is in possession of the invention claimed. See Amgen Inc. v. Chugai, *supra* at 1021, 1027.

Claims 3, 14-17, 22, 23, 25, 26, 36 and 38 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Where the invention involves a biological material and words alone cannot sufficiently describe how to make and use the invention in a reproducible manner, access to the biological material may be necessary for the satisfaction of the statutory requirements for patentability under 35 U.S.C. 112. Courts have recognized the necessity and desirability of permitting an

applicant for a patent to supplement the written disclosure in an application with a deposit of biological material which is essential to meet some requirement of the statute with respect to the claimed invention. Merck and Co., Inc. v. Chase Chemical Co., 273 F. Supp. 68, 155 USPQ 139 (D. N.J. 1967); In re Argoudelis, 434 F.2d 666, 168 USPQ 99 (CCPA 1970).

Applicant claims a plasmid construct in the instant claims. In order to sufficiently enable the claimed plasmid, Applicant must make a biological deposit. The deposit rules (37 CFR 1.801 - 1.809) set forth examining procedures and conditions of deposit which must be satisfied when a deposit is required. See MPEP 2402-2404. Applicant is directed to the attachment for further guidance.

Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4, 6, 8, 9, 14-17, 22, 23, 25, 26, 36 and 38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The instant claims are vague and indefinite as to the metes and bounds of the claim because they claim anti-angiogenic proteins, in more specific embodiments restin, and derivatives thereof. "Derived" is a term that is non-specific and relative in nature for which Applicant provides no definition. It provides no clarity as to what Applicant's claimed invention includes and what it does not include. Without a more specific definition of the claim, it is impossible to determine what and how many derivations comprise the invention. Applicant's

disclosure does not provide any definition as to the process of deriving the variants of anti-angiogenic proteins and restin nor what is included in the definition of derivatives.

The nature and number of the derivations to arrive at the invention Applicant seeks to protect with the patent are not established such that a person skilled in the art may replicate the invention without undue experimentation. The limits of the inventions cannot be discerned and others could not possibly know if they were infringing Applicant's claim. Thus, the imprecision of the claim as written makes the metes and bounds of the invention unclear such that the instant claims are rejected pursuant to 35 U.S.C. 112, second paragraph.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Konstantina Katcheves whose telephone number is (703) 305-1999. The examiner can normally be reached on Monday through Friday 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 305-7939 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 305-3388.

Konstantina Katcheves
July 30, 2001

REMY YUCEL, PH.D
PRIMARY EXAMINER